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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,777	CHENG ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,23-28,32-34 and 37* is/are pending in the application.

4a) Of the above claim(s) *32-34 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19 and 23-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18, 20-22, 29-31, 35 and 36 have been canceled. Claims 19, 23-28, 32-34 and 37 remain pending.

Applicant's arguments filed 3-6-09 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The title will have to be changed to reflect the claims, e.g. a transgenic mammal secreting B-domain deleted human FVIII in its millk.

Election/Restrictions

This application contains claims 32-34 and 37 drawn to a non-elected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 32-34 submitted 6-29-07 and claim 37 submitted 8-27-08 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The milk (claims 32-34 and 37) remains patentably distinct from the transgenic and method of making the transgenic. Inventions are related as mutually exclusive species in an intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product, and the species are patentably distinct (MPEP § 806.05(j)). In the instant case, the intermediate product (transgenic) is deemed to be useful as food and the

inventions are deemed patentably distinct because there is nothing on this record to show them to be obvious variants. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 32-34 and 37 remain withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 19 and 23-31 remain under consideration as they relate to transgenics and methods of making transgenics.

Claim Rejections - 35 USC § 112

New Matter

Claims 19 and 23-28 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not support a B-domain deleted human clotting factor VIII polypeptide having the amino acid sequence from amino acid residue 18 to amino acid residue 1448 of SEQ ID NO: 15 as newly claimed. Applicants point to pg 2, lines 2-5, which teaches a full length FVIII cDNA coding for a protein with 2351 amino acids. Applicants point to pg 19, lines 3-4, which teaches B-domain-deleted hFVIII cDNA is 4.3 kb and “truncate polypeptide (hFVAIIIΔB) is 1448 aa (SEQ ID NO: 15)”. Applicants point to SEQ ID NO: 14 and 15 and Fig. 3C. The citations provided do not teach the

species of a B-domain deleted Factor VIII having amino acid residues 18 to 1448 of SEQ ID NO: 15 as now claimed. It is not readily apparent that applicants contemplated the species of a protein comprising amino acids 18-1448 of SEQ ID NO: 15 now claimed. Accordingly, the limitation is new matter.

Indefiniteness

The previous indefiniteness rejection of claims 19 and 23-31 has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

Claims 19 and 25-28 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (Transgenic Research, 11:257-268, 2002) in view of Soukharev (Blood Cells, Molecules and Diseases, 28:234-248, 2002) and Jolly (WO 98/00541) and supported by Lubon (US Patent 6,255,554, Issued July 3, 2001).

Chen made a transgenic mouse comprising a vector encoding 7.2 kb of hFVIII coding region operably linked to the 2.0 kb bovine a-LA promoter and 19 amino acid bovine a-LA signal peptide sequence (pg 258, col. 2, first full paragraph; paragraph bridging pg 258-259). The 19 amino acid leader sequence of Chen is the 19 amino acid signal peptide of SEQ ID NO: 13 and encoded by SEQ ID NO: 1. Claim 19 only requires “a" peptide of SEQ ID NO: 14, which can be interpreted broadly. The signal peptide used by Chen meets the limitation because it contains at least one bovine α-S1 casein signal peptide of SEQ ID NO: 14. The mouse was made by introducing the transgene construct (i.e. expression cassette) into an embryo, implanting the embryo into a recipient female, allowing the embryo to develop to term, and testing the resulting

offspring and identifying mice that secreted hFVIII in milk by RT-PCR and analysis of the milk for protein (paragraph bridging columns 1 and 2 of pg 263). Chen did not delete the B-domain of hFVIII.

However, Soukharev suggested making transgenic mammals expressing B-domain deleted FVIII to improve yield of FVIII (pg 241, paragraph bridging columns 1 and 2). "[A]nother approach to improve recombinant FVIII molecule is to introduce modifications to improve its effective secretion from FVIII-expressing cell" (page 239, col. 1, paragraph 1, lines 1-4) and that "removal of the B domain...was found to dramatically improve the yield of FVIII" (page 237, col. 2, lines 3-6). Soukharev taught "an attractive possibility to increase the yield of rFVIII is to produce a biologically active form of FVIII by coexpressing its heavy and light chains" (page 239, paragraph 2, line 1 to col. 2, line 2). Without evidence to the contrary, the B-domain deleted hFVIII taught by Soukharev inherently produces a hFVIII comprising a light chain (A3-C1-C2 domain) and a heavy chain (A1-A2 domain) operably linked by a junction as in claim 25.

Thus, it was obvious to those of ordinary skill in the art at the time of filing to make a transgenic mouse encoding hFVIII as taught by Chen, wherein the hFVIII had a deletion in the B-domain as taught by Soukharev. Soukharev provides motivation to delete the B-domain to improve the yield in milk on pg 241, lines 1-5. Those of skill would have a reasonable expectation of successfully improving the yield of FVIII as suggested by Soukharev because results in vitro improved the yield (pg 237, "Genetic engineering to improve the yield of recombinant FVIII). Lubon provides further evidence

that fragments of hFVIII could be made in a non-human transgenic animal (claim 1 of Lubon).

Soukharev did not teach the B-domain deleted hFVIII polypeptide had amino acid residues 18 to 1448 of SEQ ID NO: 15 as in claim 19 as amended.

However, Jolly taught a B-domain deleted hFVIII polypeptide having amino acids 18 to 1448 of SEQ ID NO: 15 (SEQ ID NO: 47). In fact, Jolly discussed numerous B-domain deleted hFVIII known in the art for use in genetic engineering (pg 25-28).

Thus, it would have been obvious to those of ordinary skill in the art at the time the invention was made to make a transgenic mouse encoding hFVIII as taught by Chen using the B-domain deleted hFVIII SEQ ID NO: 47 described by Jolly (or any other B-domain deleted hFVIII known in the art). Those of skill would have been motivated to use SEQ ID NO: 47 of Jolly to improve the yield as suggested by Soukharev. In addition, Jolly provides evidence that the various B-domain proteins were interchangeable in genetic engineering. Finally, Jolly state the advantage of using B-domain deleted rFVIII is that B-domain deleted rFVIII appear less prone to proteolytic degradation (pg 26, lines 1-3).

Those of skill would have a reasonable expectation of successfully secreting B-domain deleted rFVIII into the milk because Chen taught the means, i.e. secretory signals and promoter, required to secrete rFVIII into the milk and because Soukharev secreted B-domain deleted rFVIII in vitro to higher yields than normal rFVIII. Furthermore, the transgene used by the combined teachings of Chen, Soukharev and Jolly has the same structure as the transgene used by applicants; therefore, the

combined teachings of Chen, Soukharev and Jolly enable secreting B-domain deleted rFVIII in milk.

Claim 27 is included because "producing up to 50 mg" per liter encompasses expressing any amount up to 50 mg/l (µg/ml) and because Chen taught an average concentration of hFVIII of 20 µg/ml. The phrase "up to 50" µg/ml encompasses 20 µg/ml taught by Chen. Claim 27 is also included because Chen taught an average concentration of hFVIII of 20 µg/ml and Soukharev taught deleting the B-domain would increase expression, which is equivalent to "up to 50 µg/ml" as claimed.

Applicants argue the combined teachings of Chen and Soukharev do not teach a mammal that releases BDD-rFVIII in milk. Applicants' argument is not persuasive. Those of skill would have a reasonable expectation of successfully secreting B-domain deleted rFVIII into the milk because Chen taught the means, i.e. secretory signals and promoter, required to secrete rFVIII into the milk and because Soukharev secreted B-domain deleted rFVIII in vitro to higher yields than normal rFVIII. There is no reason to believe the combined teachings of Chen, Soukharev and Jolly are inadequate to secrete B-domain deleted rFVIII into the milk. Furthermore, the transgene used by the combined teachings of Chen, Soukharev and Jolly has the same structure as the transgene used by applicants; therefore, the combined teachings of Chen, Soukharev and Jolly enable secreting B-domain deleted rFVIII in milk.

Applicants state Lubon did not describe a transgenic that secretes B-domain deleted rFVIII in milk. It appears that applicants argue those of ordinary skill would not have a reasonable expectation of successfully secreting B-domain deleted rFVIII in milk

because there is a different expectation of success for secreting B-domain deleted rFVIII in the milk than normal rFVIII. Applicants' argument is not persuasive. Applicants' argument is unfounded. Applicants have not provided evidence to indicate B-domain deleted rFVIII has a different expectation of successfully secreting into milk than normal rFVIII. Without evidence to the contrary, those of ordinary skill would have expected B-domain deleted rFVIII to be secreted in the milk in same manner as normal rFVIII secreted into the milk (Chen and Lubon). Furthermore, the B-domain deleted rFVIII was secreted into cells in vitro (Soukharev), which indicates B-domain deleted rFVIII was expected to be secretable. Finally, the combined teachings of Chen and Soukharev result in transgene having the same structure as the one described by applicants. Accordingly, those of ordinary skill in the art at the time of filing would have had a reasonable expectation of successfully secreting B-domain deleted rFVIII in the milk.

Applicants argue Soukharev cannot be used as art because it did not exemplify secreting B-domain deleted rFVIII in milk. Applicants' argument is not persuasive. The combined teachings of Chen, Soukharev and Jolly provide a reasonable expectation of success for reasons cited above.

Applicants argue those of ordinary skill in the art would not have had a reasonable expectation of successfully secreting B-domain deleted rFVIII in milk because up until that point B-domain deleted rFVIII had only been secreted in vitro. Applicants' argument is not persuasive. Secreting B-domain deleted rFVIII in vitro indicates the likelihood of secreting B-domain deleted rFVIII in milk.

Applicants' discussion of "fusion junctions" is noted (pg 7, last paragraph; pg 8, first paragraph); however, the claims do not require a fusion junction. If applicants' believe the fusion junction is essential to secrete B-domain deleted rFVIII in milk, clarification is required.

Overall, the claimed transgenic mammal is no different than the transgenic mouse described by the combined teachings of Chen, Soukharev and Jolly, and the combined teachings of Chen, Soukharev and Jolly provide a reasonable expectation of successfully secreting the B-domain deleted rFVIII in the milk as claimed.

Claims 19, 23, 25-28 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (Transgenic Research, 11:257-268, 2002) in view of Soukharev (Blood Cells, Molecules and Diseases, 28:234-248, 2002) and DeBoer (US Patent 5,633,076, Issued May 27, 1997) and supported by Lubon (US Patent 6,255,554, Issued July 3, 2001).

The combined teachings of Chen, Soukharev and Jolly taught a transgenic mouse comprising a vector encoding B-domain deleted hFVIII coding region comprising amino acids 18-1449 of SEQ ID NO: 15 operably linked to the 2.0 kb bovine a-LA promoter and 19 amino acid signal peptide sequence (see obviousness rejection above). The combined teachings of Chen and Soukharev did not teach replacing the 19 amino acid a-LA signal peptide of SEQ ID NO: 13 with the 15 amino acid α-S1 casein signal peptide of SEQ ID NO: 14 (encoded by SEQ ID NO: 2) as in claim 23.

However, DeBoer taught a nucleic acid construct comprising various nucleic acid elements for the optimization of producing recombinant protein in the milk of transgenic animals, said recombinant protein including FVIII (col. 7, line 12) including the alpha S1 casein secretion signal peptide (col. 7, lines 18-27). DeBoer also taught using the alpha-lactalbumin, whey acidic protein, beta-casein and alpha S1 casein (col. 2, line 53 to col. 3, line 5).

Thus, it was obvious to make a transgenic mouse encoding B-domain deleted hFVIII comprising amino acids 18-1448 of SEQ ID NO: 15 operably linked to the 2.0 kb bovine a-LA promoter and a signal peptide sequence as taught by the combined teachings of Chen, Soukharev and Jolly, wherein the signal peptide was replaced with the α-S1 casein signal peptide of SEQ ID NO: 14 (encoded by SEQ ID NO: 2). One of ordinary skill in the art would have been motivated to use the α-S1 casein signal peptide instead of the α-lactalbumin signal peptide to increase secretion of hFVIII into the milk. Those of skill would have a reasonable expectation of successfully swapping signal peptides in view of the teachings of DeBoer. Lubon provides further evidence that signal peptides could be readily swapped to increase secretion into the milk of a non-human transgenic animal. Lubon states the "[i]mportant to the present invention are regulatory sequences that direct secretion of proteins into milk and/or other body fluids of the transgenic animal. In this regard, both homologous and heterologous regulatory sequences are useful in the invention. Generally, regulatory sequences known to direct the secretion of milk proteins, such as either signal peptides from milk proteins or the nascent target polypeptide, can be used..." (col. 6, lines 45-52).

Applicants are reminded that each obviousness rejection must be argued separately. Arguments for one rejection may reference previous arguments, but arguments for the two obviousness rejections cannot be combined.

Applicants argue DeBoer does not teach B-domain deleted rFVIII. Applicants' argument is not persuasive. DeBoer need not teach all the limitations of the claims. DeBoer has been relied upon for the limitation in claim 23. Soukharev and Jolly have been relied upon for teaching the B-domain deleted rFVIII.

Claim 24 appears to be free of the prior art because the prior art did not teach or suggest the amino acid sequence of SEQ ID NO: 15.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner